REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Status of the claims

Claims 1-23 were pending in the subject application. Of these claims, the examiner had withdrawn claims 22 and 23 from consideration.

With this submission, claims 1, 2, 4, 7, 9, 10-14, 18, and 21 have been amended; claims 3, 5, 6, 8, 15-17 and 19, 20, 22, and 23 have been deleted; and no claims have been newly added. Upon entry of this paper, therefore, claims 1, 2, 4, 7, 9, 10-14, 18, and 21 will be pending and under active consideration.

Rejections under 35 U.S.C. § 103

Claims 1-15 and 17-21 stand rejected over U.S. Patent No. 6,171,586 in view of U.S. Patent No. 5,677,165. The examiner maintains that, because the '165 patent discloses the use of glutamate buffers to minimize pH changes to a solution, one of ordinary skill in the art would have been motivated to combine its teachings with antibody formulations taught in the '586 patent, with a reasonable expectation of success in doing so (Office action, item no. 4). Applicants respectfully disagree.

No motivation to modify the references as alleged

Previously, applicants have emphasized that one of ordinary skill would have found no reason to select a glutamate buffer, let alone a glutamate buffer having a pH between 4.0 and 6.0, from a virtually infinite number of combinations implicated by the '165 patent. Indeed, as was noted, the '165 patent teaches the use of "most any physiological buffer," preferring "titrate [*sic*: "citrate"], phosphate, succinate, and glutamate buffers or mixtures thereof." Col. 7, ln. 44-46. "Most preferred," in fact, is citrate buffer. *Id.* By definition, all "buffers" minimize pH changes; hence, no one of these buffers was deemed more desirable than the next.

The examiner has noted, however, that "the claimed composition is not limited to a formulation ***consisting of*** an antibody and a glutamate." Office action, page 4 (emphasis added). Rather, the examiner believes that the recited "contains" is synonymous with "comprising," an open transitional term, and that the claims thus accommodate "addition of other buffers, stabilizers, and/or excipients." *Id.*

In good faith effort to advance prosecution, applicants have revised the claims to a formulation comprising glutamate "as sole buffer." This recitation comports with the description in the specification, *e.g.*, abstract; pg. 6, ln. 17-19, and also is commensurate with applicants' proffered evidence of unexpected results achieved with the claimed invention (see below).

The examiner also has alleged that the claimed invention "is likely the product not of innovation, but of ordinary skill and common sense," in that the skilled artisan could have arrived at the claimed invention simply by "choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success [*i.e.*, 'obvious to try']." Office action, page 5. Applicants cannot agree.

First, notwithstanding "preferences" observed, the '165 patent in no way limits the genus of suitable buffers in a manner highlighting glutamate buffers; nor does the reference guide the person of ordinary skill to the presently recited pH range. On the same note, while the '586 patent may discourage the use of phosphate buffers "where a freeze-thaw stable formulation is desired," the patent goes on to teach the functional equivalence of "acetate, succinate, gluconate, histidine, citrate and other organic acid buffers." Sentence bridging col. 6-7. There is nothing in either reference delimiting the huge number of possible combinations of "organic acid buffers" taught, let alone pointing to a "finite" (sub)group that includes "glutamate" buffers.

Similarly, none of the cited references would have directed the skilled artisan to select sorbitol as an isotonizing agent. In fact, nothing in the references suggests sugar alcohols as a genus, let alone sorbitol as a species. To the contrary, the '165 patent teaches that, should a sugar alcohol be selected, "*mannitol* is most preferred." Col. 7, lines 27-30 (emphasis added).

Showing of unexpected results

Second, even if it were assumed, *arguendo*, that the skilled artisan could have deduced from the cited references a "finite" number of buffers "to try," as the examiner indicates, then the artisan still could not have foreseen or reasonably expected any advantage to accrue from the use of a glutamate-containing buffer instead of ostensibly similar buffers. In particular, the artisan would have had no reason to expect that a glutamate buffer, as presently recited, would maintain antibody stability better than "equivalent" buffers known in the prior art. This advantage of stability is reflected in present Example 5 of the specification, which evaluates the capacity of a medical formulation comprising glutamate buffer to maintain long-term stability of a constituent antibody formulated.

Unexpected results – lack of impurities formed

As presented in an accompanying Rule 132 Declaration of Mr. Eiji Sawa,[1] the long-term stability of the following formulations were considered. As elaborated below, the results further validate the unexpected nature of the superior stability demonstrated for a glutamate buffer of the invention, relative to an otherwise identical medical formulation containing citrate buffer.

	"Glutamate" buffer (invention)	"Citrate" buffer(comparison)
Antibody	10 mg/ml anti-CD40 (IgG4)	10 mg/ml anti-CD40 (IgG4)
Buffering agent	10 mM sodium ***glutamate***	10 mM sodium ***citrate***
Isotonizing agent	262 mM D-sorbitol	262 mM D-sorbitol
Surfactant	0.05 mg/ml polysorbate 80	0.05 mg/ml polysorbate 80
pH	5.5	5.5

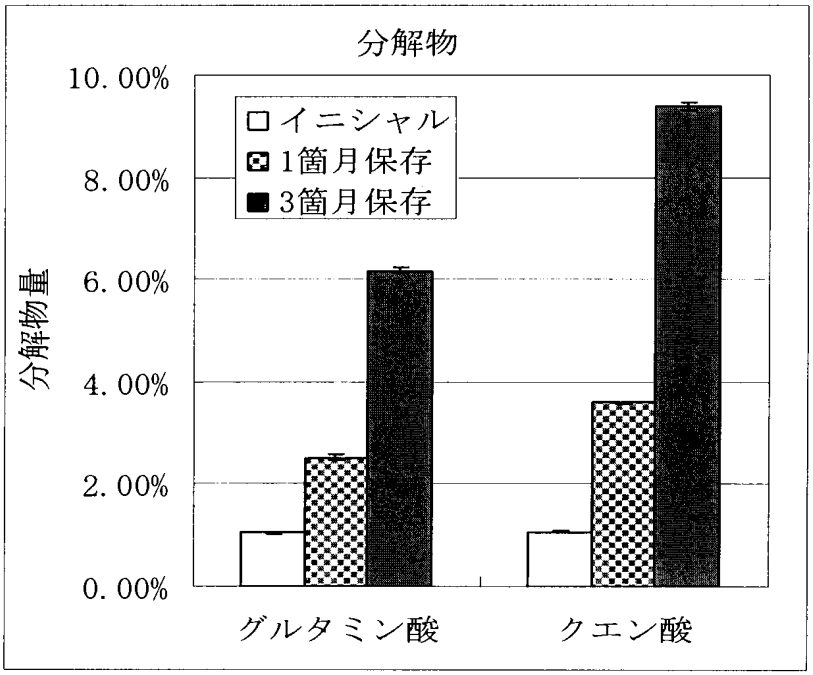
To determine their stability or "shelf-life," the respective formulations were first stored in an incubator for 12 months at 5° C. The formulations then were observed for the formation of impurities, evidenced by microscopic particles suspended in the formulation(s). Whereas impurities were readily observable in the "citrate" formulation, no impurities could be observed with the inventive "glutamate" formulation, even after one year in storage.

[1] The proffered declaration is unexecuted. Applicants will submit an executed declaration with a supplemental response.

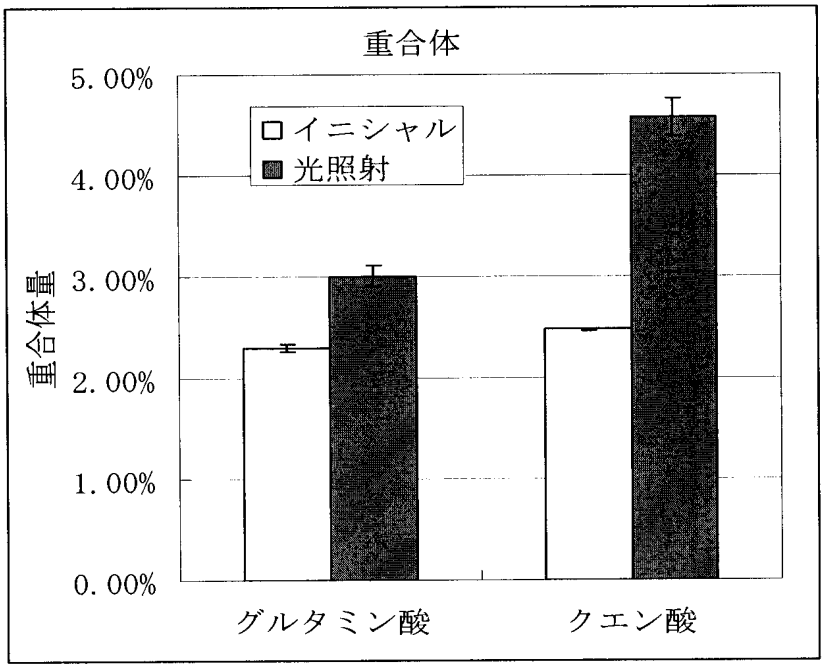
A similar study was conducted to assess the performance of the inventive buffer upon repeated freezing and thawing. In this experiment, both the "glutamate" and "citrate" buffers were subjected to three cycles of freezing (-20° C) and thawing (4° C) and observed for impurities after each cycle. Again, whereas impurities were observed in the "citrate" formulation, no impurities could be observed with the inventive "glutamate" formulation.

Unexpected results – reduced antibody aggregation and degradation

A second set of experiments to study the stability of the claimed formulation was also conducted, again with the same formulations but with IgG1 antibody, rather than IgG4 antibody. In a first assay, the amount degradation of antibodies stored in the respective formulations was determined. Both the "glutamate" and "citrate" formulations were stored under a white fluorescent lamp controlled to have approximately 4,000 lux for 300 hours. Figure 1 (immediately below) graphically illustrates that the "glutamate" buffers of the present invention were able to reduce degradation, relative to a "citrate" buffer formulation, by about 30% at both time points studied.



Yet a further study was performed to determine the ability of the respective formulations to retard or prevent aggregation. Antibodies in solution tend to aggregate over time, which is undesirable, *inter alia*, because antibody aggregation places a patient at risk of developing an immune response against the therapeutic protein.[2] The formulations were stored in an incubator at 40°C for one month and then subjected to size exclusion liquid chromatography. As illustrated in Figure 2 (below), the "glutamate" buffer according to the present invention reduced aggregation by about 34% relative to an equivalent "citrate" buffer formulation.



Lastly, the present inventors were the first to discover that a formulation comprising glutamate buffer in combination with sorbitol and a polysorbate, illustrated by polysorbate 80, can prevent aggregation of antibody, whereas a similar formulation comprising an art-recognized "equivalent," mannitol, cannot. *See* Example 3, Figure 6. Nothing in the art would could have reasonably foretold these results; indeed, the examiner has not advanced any evidence or rationale to the contrary.

[2] Draft Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins, European Medicines Agency, dated 24 January 2007 (attached herewith). *See* Section 4.1.2.

In sum, these data demonstrate both qualitative and quantitative differences, which distinguish the formulations of the present invention from those taught in the art. No reasonable permutation of teachings gleaned from the cited references could have predicted such an outcome. In fact, the art of record taught the opposite, namely, the functional ***equivalence*** of the buffers and isotonizing agents of the present invention and those of the art. Indeed, applicants were the first to discover and disclose the "preferential" use of both glutamic acid and sorbitol in the claimed formulations. *See* specification at page 24 in the 3rd paragraph ("most preferably, glutamic acid is used as a buffer agent").

Unexpected results – commensurate with claim scope

With reference to the "unexpectedness" of results discussed above, applicants further submit that the present claims are commensurate in scope with the proffered evidence. In an effort to speed prosecution, that is, applicants have tailored the claims to comport with the formulations and the antibody used in the studies presented. Thus, the present claims are directed to a formulation, with a pH between 4.0 and 6.0 and glutamate as the sole buffer, that further contains an antibody against CD40, sorbitol as an isotonizing agent, and a polysorbate as a surfactant.

Thus, the declaration evidence demonstrates results, obtained with the invention as claimed, that would have been unexpected at the time that invention was made. Accordingly, the obviousness rejection is unsustainable and should be withdrawn.

As a final matter, claim 16 stands separately rejected over the '586 patent and the '165 patent in view of U.S. Patent No. 6,416,958. The '958 patent is invoked for its disclosure of a therapeutic composition comprising a HLA-DR antibody. Office action, item No. 6. Without acquiescing to the propriety of the rejection, but rather solely to advance prosecution, applicants have canceled claims 16, mooting the rejection.

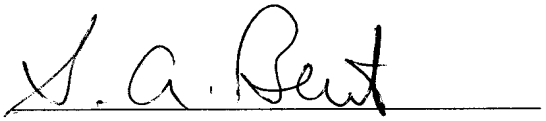
Conclusion

Applicants submit that this application is in condition for allowance, and they request an early indication to this effect. Examiner Kim is invited to contact the undersigned directly, should he feel that any issue warrants further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

Date: October 19, 2009

By 

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5404
Facsimile: (202) 672-5399

Stephen A. Bent
Registration No. 29,768

Sunit Talapatra, Ph.D.
Registration No. 54,482